new matter has been added. The amendments made herein are made for purposes of clarification and consistency among the claims, do not narrow the claims, and are not for reasons substantially related to patentability.

Formalities:

Applicant notes the Office Action deemed the title not descriptive of the invention. Applicant has amended the title to be further descriptive of the claimed invention. The Office Action also notes the use of trademarks in the specification and requests capitalization. To comply with these formal requirements, and as reflected above, Applicant submits herewith, a substitute specification to reflect the amended title and the capitalized trademarks, as well as to correct any other typographical errors as requested by the examiner.

Formal drawings have been submitted to the Official Draftsperson in accordance with the rules.

Rejections under 35 U.S.C. §112, first paragraph: Lack of Enablement

Claims 1, 2, 4, and 10-15 stand rejected under 35 U.S.C. §112, first paragraph because the specification allegedly does not enable one of skill in the art to make and use the invention. The Office Action asserts that one of skill in the art would not be able to practice the invention without undue experimentation. The Office Action does not acknowledge any scope of enablement. Applicant respectfully traverses this rejection.

The question of enablement is a question of law, based on underlying factual determination. Amgen, Inc. v. Hoechst Marion Roussel, Inc. *et al.*, No. 01-1191, 01-1218, 2003 U.S. App. LEXIS 118 at *48 (Fed. Cir. 2003). Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. The examiner should always look for enabled, allowable subject matter and communicate to applicants what that subject matter is at the earliest point possible in the prosecution of the application. (MPEP 2164.04)

The Federal Circuit has consistently held that "the specification must teach those of ordinary skill in the art how to make and use the full scope of **the invention** without undue experimentation. In re Wright, 999 F.2d 1557,1561(Fed. Cir. 1993). Since the invention is obviously that for which patent protection is sought, "the claims must be analyzed first in order to determine exactly what subject matter they encompass." In re Angstadt, 537 F.2d 498,501 (CCPA 1976). The subject matter there set out must be presumed, in the absence of evidence to the contrary, to be that "which the applicant regards as his invention." Full effect must be given to all claim limitations. Id.

The fact that a quantity of experimentation, even complex experimentation, may be required is not dispositive of the analysis (MPEP 2164.04). The key word is "undue," not "experimentation". Angstadt, 537 F.2d at 504. The factors to be considered in determining whether experimentation is undue include the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Nevertheless, not everything necessary to practice the invention need be disclosed. The Federal Circuit has stated that what is well-known is best omitted. In re Buchner, 929 F.2d 660, 661 (Fed. Cir. 1991). Further, the scope of enablement must only bear a reasonable connection to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839 (CCPA 1970). Additionally, as the Federal Circuit recently reiterated, the law is clear that the specification need teach only one mode of making and using a claimed invention. Amgen, 2003 U.S. App. LEXIS 118 at *50.

A. The Claims Do Not Require Modified Antibodies; Alternative Methods Are Taught.

The Office Action alleges that there is insufficient guidance and direction as to how to make an antibody that has reduced binding affinity for FcγRIIB due to modification of the Fc region of the antibody, while retaining or enhancing binding to

FcγRIIA and FcγRIIA, and the use of such antibodies in a method which comprises disrupting activation of SH2 domain containing inositol 5-phosphate (SHIP) by FcγRIIB.

As a preliminary matter, Applicant notes that the Office Action has construed the claims to require antibodies modified in their Fc regions so as to reduce binding affinity for FcγRIIB; however, the claims under consideration are clearly directed to a method of enhancing cytoxicity which do not *require* such antibodies. As set forth in claim 1, the claims are generally directed to methods of enhancing cytotoxicity elicited by a therapeutic antibody in a subject wherein the method comprises the step of disrupting activation of SHIP by Fc-gamma receptor IIB (FcγRIIB). Claim 2, is further directed to such methods wherein the SHIP activation results from antibody binding to FcγRIIB. Claim 2 does not further limit the methods of *disrupting* the activation of SHIP, but only adds a limitation which requires that the SHIP activation *result from* antibody binding to FcγRIIB. The therapeutic antibody which elicits the cytotoxicity in claims 1 and 2 need not be modified. Claim 4 is directed to methods wherein the antibody binding to FcγRIIB is inhibited by modifying the Fc region of the antibody to reduce its affinity for FcγRIIB. Claims 10-15 depend from either claim 1 or claim 2 (not from claim 4) and do not require a modified antibody to practice the claimed methods. Thus, claim 4 alone requires a modified antibody and Applicant respectfully asserts that the rejection for lack of enablement made in the Office Action should solely be directed to that claim.

Applicant further asserts that the claims are fully enabled as written. The specification provides sufficient guidance to enable those of skill in the art to practice the claimed methods. The Office Action fails to establish that the requirements of 35 U.S.C. §112, first paragraph have not been met.

It is respectfully submitted that the Office Action's conclusion that there is insufficient guidance and direction as to how to make an antibody that has a reduced binding affinity for FcγRIIB is misplaced, as the instant claims, are plainly directed to methods of enhancing cytotoxicity, which do not require a modified antibody. In any event, the ample instructions as to how to make and use the modified antibodies are

enabling to those of skill in the art. When the claims are properly construed, only claim 4 can fairly be stated to, in any way, require an antibody modified in the Fc region so as to reduce binding affinity to FcγRIIB and thereby disrupt activation of SHIP by FcγRIIB.

Claim 1, as stated above, is directed to methods which enhance therapeutic antibody-mediated cytotoxicity by disrupting activation of SHIP by Fc-gamma-receptor. While some of the methods of disrupting activation of SHIP, including a disclosed preferred embodiment, encompass use of modified antibodies, the specification teaches several alternative methods. All that is required is the step of disrupting activation of SHIP by Fc-gamma-receptor.

For example, the specification teaches competitive inhibition of FcγRIIB wherein a competitive inhibitor binds specifically to FcγRIIB without activating it, thereby preventing binding by a tumor-specific antibody. Examples are given including: binding of monomeric molecules to prevent crosslinking of the receptor, anti-FcγRIIB antibodies (preferably Fv antibodies) and peptides corresponding to the FcγRIIB-binding sequence of immunoglobulins, and use of small molecular weight inhibitors of FcγRIIB binding site. (Applicant's Specification, page 13, lines 10-19).

The specification also teaches methods of enhancing antibody-mediated cytotoxicity by disrupting activation of SHIP by Fc-gamma-receptor though the use of molecules directed at targeting SHIP, such as competitive inhibitors of SHIP. In the presence of such competitive inhibitors, SHIP is not capable of activation by Fc-gamma-receptor. Examples of competitive inhibitors of inositol phosphatase activity of SHIP include small molecular weight antagonists as well as antibodies. (Id. at page 13, lines 19-26).

Inhibiting the expression of FcγRIIB or SHIP is also taught in the instant specification as methods for disrupting activation of SHIP by Fc-gamma-receptor. The specification provides enabling guidance to one of skill as to how to practice the methods including the use of antisense molecules and techniques, the use of synthetic oligonucleotides, and the use of intracellular antibodies which inhibit expression or

function of the proteins involved. Also disclosed are methods for enhancing antibody-mediated cytotoxicity by disrupting the activation of SHIP by Fc-gamma-receptor which entail inhibiting signal transduction, for example via inhibitors of the distinctive inositol phosphatase activity of SHIP, or mutation of the phosphatase activity. (Specification, pages 15-18).

B. The Specification is Enabling for Antibodies Modified in Their Fc Regions for Reduced Affinity Binding of FcγRIIB.

Notwithstanding the above discussion relating to the teaching of a variety of alternatives to the use of modified antibodies for practicing the claimed methods of disrupting the activation of SHIP by Fc-gamma-receptor, Applicant further respectfully asserts that the instant specification is enabling for a variety of antibodies and provides ample guidance to those of skill in the art on the making and using of antibodies modified in the Fc region such that they have reduced binding for FcγRII.

In fact, as can be seen in throughout the specification, clear directions as to how to make and use the antibodies required to practice claim 4 are provided. For example, the teachings on page 13, line 27 through page 15, line 26 provide guidance sufficient to enable one of skill in the art to make and use antibodies with modified Fc regions. Multiple patents and other publications are incorporated by reference to provide more specific guidance on modifying the Fc region to create antibody variants. Given the high level of skill in the art, and the ready availability of kits for conducting the basic steps, the specification, particularly the material incorporated by reference, and the teachings at page 15, lines 22-26, combined with the working examples 1, 2, and 3, is more than sufficient to satisfy the requirements of 35 U.S.C. §112.

For example, the engineering of D265A mutant antibody is described on page 32, lines 1-15, and supplemented as discussed above on page 35, lines 3-21. In addition to directions for making the antibodies, methods for screening antibodies for both the required properties, as well as the preferred properties, are provided. The methods include the use of known, recombinant FcR molecules. From these

teachings alone, one of skill in the art would be able to follow the guidance provided and make the desired antibodies.

Example 2 details the generation of IgG1 Fc domains with reduced binding to FcRIIB in yeast surface display systems, as well as the generation of differential interaction of IgG1 Fc with RIIA, RIIIA and RIIB. Also disclosed are variants with enhanced RIIB, RIIIA or RIIIB binding. Methods of screening include receptor-coated plate assays, and panning or flow cytometry using, for example, FITC-labelled recombinant FcRIIB. Alternatively, screening was accomplished by panning mutagenized fusion libraries on plates onto which recombinant receptors were immobilized – this method was useful for identifying mutant Fc containing antibodies which retained RIIA binding with reduced or eliminated RIIB binding. (Specification at page 35, line 10; page 37, lines 11-27). Procedures for obtaining monoclonal antibodies with the desired properties are provided in Example 3.

Applicant respectfully submits that these teachings, taken as a whole, would enable one of skill in the art to make and use the antibodies required by claim 4. There is ample guidance as to where and how to make any desired changes. Sequences are described and incorporated by reference. Multiple techniques for making the modifications are provided and as discussed above, simple methods for screening clonal populations of monoclonal antibodies, or libraries containing the modified Fc regions are also provided to allow for selection of antibodies with the desired properties. Collectively, these teachings would render any experimentation routine and place the antibodies well within the grasp of those of skill in the art. Thus, it is respectfully submitted that the Office Action fails to establish a proper case for lack of enablement, as one of skill in the art is plainly provided adequate guidance as to how to make and use the antibodies.

C. The Additional Bases for the Rejection, Including the References Cited, do not Support a Prima Facie Case for Lack of Enablement.

The Office Action states, as support for the rejection, that the specification discloses that FcγRIIB makes a dominant contribution to antibody-mediated cytotoxicity and that disrupting FcγRIIB activation greatly improves cytotoxicity.

The Office Action further states that the specification discloses that to practice the invention it would be "essential" that the antibodies, while having reduced binding affinity for FcγRIIB due to modification of the Fc region of the antibody, retain or have enhanced binding to FcγRIIA and FcγRIIIA, and that the specification does not provide sufficient guidance and examples as to which modifications would be acceptable to retain these specific structural and functional properties of the antibodies (referred to in the Office Action as "claimed antibodies" notwithstanding the fact that no claims to antibodies are under consideration in the application in view of the restriction requirement) to be used in the claimed method for enhancing cytoxicity.

In an attempt to support the rejection for lack of enablement, the Office Action states that applicant acknowledges, on page 35, lines 5-20 of the specification, that a single amino acid replacement in the Fc region of the mouse anti-HER2 antibody, 4D5, reduces affinity for both FcγRII and FcγRIII receptors. In a further attempt to bolster its position, the Office Action cites the following references: Colman *et al.* (Research in Immunology 145: 33-36, 1994) for the proposition that a single amino acid change in an antigen can effectively abolish antibody-antigen binding; Abaza *et al.* (J. Protein Chemistry 11: 433-444, 1992) for the proposition that a single amino acid substitution outside the antigenic site on a protein effects antibody binding; Lederman *et al.* (Mol. Immunol. 28: 1171-1181, 1991) for the proposition that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody; and Li *et al.* (PNAS 77: 3211-3214, 1980) for the proposition that immunoreactivity can be dissociated from other biological activities.

The Office Action alleges that undue experimentation would be necessary to determine which modifications would be acceptable to retain "occluding structural and functional activity" given that the relationship between the sequence of a protein and its tertiary structure are not well understood and are not predictable. In support of this, Ngo et al. (Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox, Chapter 14 in The Protein Folding Problem and Tertiary Structure Prediction, Merz and Le Grand (Eds)) are cited.

The Office Action states that the specification discloses that FcγRIIB makes a dominant contribution to antibody-mediated cytotoxicity and that disrupting FcγRIIB activation greatly improves cytotoxicity. The specification states that "the *in vivo* date were critical to the discovery that FcγRIIB makes a dominant contribution to antibody-mediated cytotoxicity, and that disrupting FcγRIIB greatly improves cytotoxicity." This emphasizes the significance that the instant applicant provides *in vivo* data in support of the claimed methods. The in vivo data were "critical" in that the *in vitro* and *in vivo* experiments did not necessarily reveal the same things about therapeutic antibody cytotoxicity. The statement, however, simply cannot be construed to limit the claimed invention to methods in which a modified antibody is required, or to limit the claims in any way. As discussed previously, there are several alternative methods provided by which one of skill can utilize the Applicant's discovery to practice methods of disrupting the activation of SHIP by FcγRIIB. From the Applicant's disclosure, those of skill in art would understand the significance of the role of FcγRIIB in activating SHIP which in turn inhibits the cytotoxic effect of therapeutic antibodies. Any method by which this inhibitory effect can be relieved or diminished will have the effect of enhancing cytotoxicity and the practice of these methods by those of skill in the art is clearly enabled by the instant specification.

The Office Action alleges that the specification discloses (at page 7, lines 10-15) that to practice the invention it would be *essential* that the antibodies, while having reduced binding affinity for FcγRIIB due to modification of the Fc region of the antibody, retain or have enhanced binding to FcγRIIA and FcγRIIIA. (emphasis added). Applicant respectfully calls the Examiner's attention to the cited section again, as it simply does not make any statement as to the essential nature of antibodies to the claimed method. The section states:

> "Enhancing cytotoxicity elicited by a therapeutic antibody *in vivo* in a human comprises disrupting activation of SHIP by Fc-gamma-receptor IIB (FcγRIIB or FcRIIB). In particular, by disrupting therapeutic antibody binding to the inhibitory Fc receptor FcγRIIB while retaining or enhancing binding to FcγRIIA and FcγRIIIA, or by preventing FcγRIIB

from activating SHIP, the invention significantly improves antibody efficacy."

Applicant respectfully submits that nothing in the cited portion of the specification can be read to limit the invention to an essential mode of operation, while Applicant has already noted that using such antibodies is one preferred embodiment. (*See* Specification at page 13, line 27 to page 15, line 26). The Office Action's citation of these statements from the instant specification does nothing to further the examiner's burden in establishing a lack of enablement of antibodies modified in their Fc regions for reduced affinity binding of FcγRIIB.

Turning next to the Office Action's assertion that applicant acknowledges, on page 35, lines 5-20 of the specification, that a single amino acid replacement in the Fc region of the mouse anti-HER2 antibody, 4D5, reduces affinity for both FcγRII and FcγRIII receptors, Applicant notes that claim 4 requires only that the antibody's binding to FcγRIIB is inhibited by reducing the antibody's affinity for FcγRIIB by modifying the Fc region of the antibody. While Example 2 is set forth to help establish the importance of the role of FcγR, for example in the *in vivo* anti-tumor effects of a therapeutic antibody, as discussed *supra*, the claims do not require that the antibody have any particular properties with respect to FcγRIII receptors. Provided that an antibody is modified in the Fc region to have a reduced affinity for FcγRIIB, and that it disrupts the activation of SHIP by FcγRIIB, it satisfies the requirements of claim 4 with respect to the modified antibody. Limitations regarding FcγRIII must not be imported from the specification into the claims, "to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." (MPEP 2111; In re Prater, 415 F.2d 1393, 1404-05 (CCPA 1969).

Addressing now the references cited by the Office Action to support the alleged lack of enablement rejection, Applicant responds in turn to each.

The Office Action states that Colman *et al.* teach that a single amino acid change in an antigen can effectively abolish antibody-antigen binding. While Colman *et al.* may help establish a certain level of unpredictability in the art of antigen

modification or antigenic variation relating to antigen-antibody binding, the current claims are not predicated on any changes to antigens, or the Fab region of the antibody. Colman *et al.* do not address the predictability of modifying the Fc portion of an antibody to reduce its affinity for FcγRIIB. Further, the present invention in no way relates to modifying an antigen to alter antibody-antigen binding. The specification expressly states, for example that antibody D265A was engineered "while retaining its affinity for its cognate antigen p185 HER-2/neu." (Specification at page 35, lines 6-7).

Applicant respectfully submits that one of skill in the art would not reasonably expect a modification in the Fc region of an antibody to have an impact on the antigen binding. Such an expectation is contrary to the teachings of the art. Effector functions mediated by the Fc region are divided into those which operate *after* the binding of antibody to antigen and those that operate *independent of* antigen binding. (Id. at page 2, lines 16-22, emphasis added). Likewise, in Example 1, the specification teaches "[S]ince the mutation would not be expected to disrupt antibody-antigen interactions, as predicted, both 4D5 and D265A antibodies purified from transfected cell supernatants bound cellular p185HER-2/neu with equivalent avidity. . ." (Id. at page 35, line 14-17). With respect to alterations within the antibody, Colman *et al.* teach that antibody-antigen interfaces should not be more sensitive to amino acid substitutions than other protein-protein interfaces.

Similarly, Abaza *et al.* allegedly teach that a single amino acid substitution outside the antigenic site on a protein effects antibody binding. While potentially establishing a certain level of unpredictability regarding amino acid substitutions in an antigen as relates to binding by monoclonal antibodies, Abazza *et al.* do not address the predictability of modifying the Fc portion of an antibody to reduce affinity for the FcγRIIB. Again the art teaches that effector functions and antigen-antibody are independent. The underlying principle of Fc domain mutagenesis exploits the expression of the dimeric Fc domain in an expression system (Id. at page 36, lines 22-25), and thus, could not result in modification to the antigen, and would not result in modification to those portions of the antibody involved with antigen binding.

It will be appreciated that the above argument applies with equal force to the cited publications from Lederman *et al.* and Li *et al.* each of which teaches amino acid alterations within an antigen and the corresponding negative effect on binding by an antibody. Again, these references can not be construed to address predictability of modifying the Fc portion of an antibody to reduce affinity for the FcγRIIB. For all of the above reasons, these publications also do not advance the Office Action's assertion that the current claims are not adequately enabled so as to teach those of skill how to make and use antibodies for use in accordance with the method of claim 4. The cited references do not address predictability in modifying Fc regions of antibodies; they do not address predictability in binding interactions with FcR receptors; nor do they touch on enhancing cytotoxicity or disrupting SHIP activation. They do not identify what information is allegedly missing from the instant specification, or why one skilled in the art could not supply the information without undue experimentation and they provide no specific technical reasons for the rejection. The cited art does not advance the position taken as to unpredictability in the relevant art, and here, simply cannot support a *prima facie* case of lack of enablement.

Finally, the Office Action points generally to Merz *et al.* for the proposition that undue experimentation would be required to determine which modification would be acceptable to retain occluding structural and functional activity, in view of the fact that the relationship between the sequence of protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable. Significantly, Applicant notes that the 3D structure of the Fc region of the human IgG is known from the crystal structure, thus rendering moot any concerns regarding the need to predict the tertiary structure. (Specification at page 2, lines 13-14). Merz *et al.* consider the problem of developing an algorithm for predicting the structure of a given protein from it amino acid sequence alone. They do not completely rule out the existence of a global protein-structure prediction algorithm that is both efficient and correct. They further note that in more reasonably-defined circumstances, the problem may be efficiently solvable.

Additionally, Merz *et al.* was published in 1994; during the intervening years between its publication and the filing of the instant application, many advances have been made, for example, in computational capacity and understanding of various aspects of protein structure. Applicant includes copies herewith of references by DeGrado (Science 278: 80-81, 1997) and Dahiyat and Mayo (Science 278: 82-87, 1997) as evidence of some of the advances in computational design algorithms which have enabled design, including *de novo* design, of stable new proteins as well as the screening of 1.9×10^{27} possible amino acid sequences for compatibility with a target. Applicant also cites Service (Science 277: 179, 1997) for the proposition that a protein's amino acid sequence may be altered by up to 70%, yet virtually always folds up into the same 3D structure. A copy is provided herewith.

Merz *et al.* do not address the problems of selecting an amino acid residue to modify, or modifying the Fc region of an antibody. In short, Merz *et al.* reflect the 1994 state of the art in mathematically predicting 3D protein structures from amino acid sequences; but Merz *et al.* do not inform as to the predictability of problems reasonably related to those faced by one of skill in art seeking to practice the claimed invention.

In sum, with respect to the rejection for the lack of enablement, it is respectfully submitted that the Office Action does not establish any grounds to support the contention that undue experimentation would be required, or that insufficient guidance is provided to enable those of skill in the art to make and use the invention as claimed. The Applicant asserts that the claims, as amended are fully enabled in accordance with 35 U.S.C. §112 and that no undue experimentation is required for a skilled artisan to practice claim 4 or any of the claims. Accordingly, Applicant respectfully requests withdrawal of the rejection for lack of enablement under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, first paragraph: Written Description

Claims 1, 2, 4, and 10-15 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was in possession of the claimed invention at the time of filing. Applicant respectfully traverses this rejection.

The adequacy of a written description is a question of fact which must be determined on a case-by case basis. MPEP 2163. A written description is given a strong presumption of adequacy and rejection of original claims for lack of written description should be rare. Id. An examiner must overcome the presumption of adequacy by putting forth, on a reasonable basis, sufficient evidence or reasoning. In re Wertheim, 541 F.2d 257, 263 (CCPA 1976). Arguing lack of literal support is not enough since the invention need not be described in *ipsis verbis* to satisfy the written description requirement. Id. at 265.

As the Federal Circuit has stated: ". . .the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. *et al.* v. Mahurkar *et al.*, 935 F.2d 1555, 1563-4 (Fed. Cir. 1991) (emphasis in original). See also Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1566 (Fed. Cir. 1997). A preponderance of evidence is required as to why a skilled artisan would not recognize a description of the claimed invention, as that is the perspective from which satisfaction of the requirement is measured. Amgen Inc. v. Hoechst Marion Roussel, Inc. *et al.*, No. 01-1191, 01-1218, 2003 U.S. App. LEXIS 118 at *35 (Fed. Cir. 2003) citing Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997); see also MPEP 2163. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim. Id. at *39.

Possession of the invention may be established through words, structures, figures, diagrams and formulas which fully set forth the claimed invention. Lockwood, 107 F.3d at 1572. "Generally there is an inverse correlation between the

level of skill and knowledge in the art and the specificity of the disclosure necessary to satisfy the written description requirement." MPEP 2163.

Applicant again notes, as a threshold matter, that the Office Action has construed the claims to encompass a genus of antibodies that, due to modification of the Fc portion of the antibody, have reduced binding affinity for FcγRIIB while retaining or enhancing binding to FcγRIIA and FcγRIIIA for use in a method for enhancing cytotoxicity elicited by the antibody *in vivo* wherein the method comprises disrupting the activation of SHIP by FcγRIIB. Applicant respectfully asserts, as detailed above, and reiterated here for convenience, that the claims are generally directed to methods of enhancing cytotoxicity elicited by a therapeutic antibody in a subject wherein the method comprises the step of disrupting activation of SHIP by Fc-gamma receptor IIB (FcγRIIB). Claim 2, is further directed to such methods wherein the SHIP activation results from antibody binding to FcγRIIB. Claim 2 does not further limit the methods of *disrupting* the activation of SHIP, but only adds a limitation which requires that the SHIP activation *result from* antibody binding to FcγRIIB. The therapeutic antibody which elicits the cytotoxicity in claims 1 and 2 need not be modified, and therapeutic antibodies capable of satisfying the requirements of claims 1 and 2 are known in the art. Claim 4 is directed to methods wherein the antibody binding to FcγRIIB is inhibited by modifying the Fc region of the antibody to reduce its affinity for FcγRIIB. Claims 10-15 depend from either claim 1 or claim 2 (not from claim 4) and do not require a modified antibody to practice the claimed methods. Thus, claim 4 alone *requires* a modified antibody and Applicant asserts that any written description rejection made on the basis provided in the Office Action should solely be directed to that claim.

The Office Action cites several cases to support the alleged failure to satisfy the written description requirement. In particular, the Office Action cites Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993), concluding therefrom that the invention claimed in the instant application can not have been conceived until a representative description of the structural and functional properties of the claimed invention has occurred; that the written description requires more than a mere statement that the

[what is claimed] is part of the invention; and that sequences themselves are required for the antibodies. Eli Lilly, 119 F.3d at 1569 (Fed. Cir. 1997) is cited for the proposition that a description of the genus may be achieved by means of a recitation of a representative number of antibodies falling with the scope of the genus, or by means of a recitation of structural features common to the genus which features constitute a substantial portion of the genus. Finally, the Office Action cites Vas-Cath, 935 F.2d at 1555 which stated the specification must allow persons of ordinary skill in the art to recognize that the inventor invented what is now claimed.

Applicant respectfully submits that the Office Action's reliance on Fiers and Eli Lilly are misplaced. The holdings in those cases, are limited to their facts - specifically to situations where claims are directed to DNA or cDNA. Moreover, with respect to Fiers, the Office Action's statements regarding conception are also misplaced. The court's comments regarding conception of the invention were appropriate in the context of an interference where a party tried to establish a prior date of invention. It is respectfully submitted that these same remarks make no sense in the context of normal patent prosecution, where, as here, the inventors have reduced their invention to practice, both actually and constructively, in writing the application. The patent's specification is on its face a clear record of "the mental act and the definite and permanent idea of the complete and operative invention as it is to be hereafter to be applied in practice." MPEP 2138.04

Further, the position taken by the Federal Circuit in those cases was that *where the claimed inventions were **DNA**s*, in the absence of adequate descriptions of the DNAs, sequences themselves were required to satisfy the written description requirements. The Federal Circuit has steadfastly refused to generalize that holding, clarifying "[M]ore recently in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." Amgen, 2003 U.S. App. LEXIS 118 at *41.

Here, claims are not directed to DNAs. The claims are to methods of enhancing cytotoxicity. The modified antibodies used with the present invention are readily understood by those of skill in the art. Here, in accordance with the holding in

Amgen, sufficient information has been conveyed such that those of skill in the art would recognize the description of the molecules. The specification conveys, to those of skill in the art, distinguishing information concerning the identity of the molecules such that one of skill could visualize or recognize the identity of the members of the genus of antibodies so-modified. Nothing more is required.

Applicant respectfully submits that the Office Action, in inadequately or improperly construing the subject matter covered by the claims as a whole, has failed to properly determine the adequacy of the written description according the "Written Description" Requirement Guidelines. As a result, the Office Action necessarily failed to properly weigh all factors including partial structure, physical/chemical properties, functional characteristics, known or disclosed correlations between structure and functions, methods of making, and combinations of the above in view of the level of skill and knowledge in the art in determining whether one of skill would recognize that applicant was in possession of the invention. The specification describes the modified antibodies sufficiently so as to satisfy the requirements 35 U.S.C. §112, as well as the policies behind it. The specification clearly conveys that the Applicant has invented the claimed subject matter; the public is put in possession of what was invented; and there is a *quid pro quo* for the patent rights sought. In view of the foregoing, the Applicant respectfully requests the withdrawal of the rejection for lack of adequate written description under 35 U.S.C. §112.

Other Claim Amendments:

Claims 1, 2, and 4 have been amended to clarify the claimed invention, or to achieve an overall consistency among the claims. These amendments do not narrow the scope claims, and are not for reasons substantially related to patentability.

Summary

In view of the foregoing amendments and remarks, Applicant asserts that the claims are in condition for allowance. Early and favorable action, and notification of allowance is earnestly solicited. If it would expedite prosecution of this application, the Examiner is invited to confer with Applicant's undersigned representative.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

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Date:

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (Amended) 1. A method for enhancing cytotoxicity elicited by a therapeutic antibody ~~*in vivo*~~ in a subject, which method comprises disrupting activation of SHIP by Fc-gamma-receptor IIB (FcγRIIB).

2. (Amended) The method according to claim 1, wherein activation of SHIP ~~the SHIP activation~~ by FcγRIIB results from antibody binding to FcγRIIB.

4. (Amended) The method according to claim 2, wherein antibody binding is inhibited by modifying the Fc ~~portion~~ region of the antibody to reduce its affinity for FcγRIIB.